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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/619,939	DRAGHIA-AKLI ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *21-23,25-28,30 and 31* is/are withdrawn from consideration.

5)☒ Claim(s) *29* is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☒ Claim(s) *24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 27 November 2006 in response to the Non-Final Office Action mailed 24 August 2006. Claims 21-23, 25-28, 30 and 31 were withdrawn from consideration and claims 1-20, 24 and 29 were considered in the 24 August Office Action. Claims 1, 4, 6, 8, 10, 13-16, 18, 19 and 21-31 were amended in the 27 November Paper. Claims 1-31 are pending and claims 1-20, 24 and 29 are under consideration.

Response to Amendment and Arguments

Specification

Objection to the disclosure for the reasons set forth at pages 2-3 of the 24 August Office Action is **withdrawn** in view of the amendments to the specification.

Claim Objections

Objection to claims 4, 6, 8, 10, 13, 14, 24 and 29 for the reasons set forth at page 3 of the 24 August Office Action is **withdrawn** in view of the claim amendments.

Claim Rejections - 35 USC § 112, first paragraph

Claims 1-17, 19 and 20 **stand rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a synthetic mammalian expression plasmid utilized for plasmid mediated gene supplementation, wherein the plasmid comprises a nucleic acid encoding GHRH, does not reasonably provide enablement for any synthetic mammalian expression plasmid having the features recited in the claims and useful for plasmid mediated gene

supplementation. This rejection is maintained for the reasons set forth in the 24 August Office Action at pages 3-11 and herein below in the response to Applicant's arguments. As stated in the Office Action,

> [T]he art evidences that useful gene supplementation was not routinely practiced in the art at the time of filing and, given that each therapeutic gene sequence and gene supplementation protocol presents unique challenges, enablement for any given mammalian expression plasmid construct for use in gene supplementation cannot be predictably extrapolated to gene supplementation using other therapeutic gene sequences. As the teachings of the instant disclosure provide no guidance that would enable the skilled artisan to use any eukaryotic therapeutic gene sequence for plasmid gene sequence other than GHRH, making and using what is claimed beyond the scope of a mammalian expression vector comprising a nucleic acid encoding GHRH would require undue experimentation. Therefore, the claims are properly rejected under 35 USC §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

Response to Arguments

In response to the *prima facie* rejection of record, Applicant first contends that examples of expression plasmids other than those encoding GHRH are found in the specification. Applicant particularly points to discussion relating to growth hormone and IGF-I in the specification and publications describing plasmids encoding IL-5, CT-1 and various reporter genes. However, it is noted that none of the cited teachings evidence that the claimed expression plasmids are enabled for use in gene supplementation as broadly as is claimed. The teachings of the specification relating to growth hormone and IGF-1 have to do with their role in immune function and growth hormone therapy via administration of recombinant protein. These teachings are not directed to plasmid mediated gene replacement. Likewise, the art having to do with expression of bacterial or insect proteins as reporter genes does not evidence enabled gene replacement therapy. Although Aihara does teach plasmid mediated expression of IL-5 in mouse muscle and Lesbordes teaches that *in vivo* electrotransfer of the cardiotrophin-1 gene into

skeletal muscle slows down progression of motor neuron degeneration in the progressive motor neuronopathy (*pmn*) mouse, these teachings and the teachings of the instant application would not enable the skilled artisan to make and use a synthetic expression plasmid for plasmid mediated gene supplementation as broadly as claimed. As pointed out in the previous Office Action, the claims encompass a plasmid vector comprising any therapeutic gene sequence, wherein the construct is to be used for plasmid mediated gene supplementation. Even if one were to take the teachings Aihara and Lesbordes as examples of fully enabled gene supplementation, *arguendo*, one would not conclude that gene supplementation is generally enabled, regardless of the therapeutic gene sequence comprised by the plasmid, in view of the general unpredictability of the art evidenced in the previous Office Action.

Next, Applicant dismisses the art cited in the previous Office Action as outdated. However, Applicant fails to provide any evidence that this is the case. The Office Action cites numerous publications spanning a critical period in the development of the gene therapy art, which publications evidence numerous problems encountered in developing technologies for gene therapy and gene replacement. There is nothing of record to suggest that in the approximately 1 year between the publication of Rubanyi et al. and the effective filing date of the instant application gene replacement became fully enabled such that one could use the invention as stated in the claims, irrespective of the therapeutic gene sequence, without undue experimentation.

Applicant further dismisses the art cited in the Office Action as irrelevant because the claims do not pertain to methods of delivery but rather to a synthetic mammalian expression plasmid optimized for length and strength of expression.

This argument is not persuasive because, as pointed out in the previous Office Action, when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

Applicant also contends that the claimed invention solves the problems of the prior art by providing "optimized" synthetic plasmids. However, it is noted that "optimization" of the plasmid as claimed constitutes no more than a single silent mutation within the coding sequence. There is nothing of record to suggest that modifying a single codon would be sufficient to overcome the complications that have plagued the gene therapy art for many years as evidenced by the art cited in the Office Action.

Applicant dismisses each of the publications cited in the Office Action on various grounds. Applicant contends that Verma, Marshall and Ross are irrelevant because delivery is not relevant to the instant claims. However, as discussed above, delivery is relevant to the claims in view of the fact that the claims recite that the vector is to be used for gene supplementation.

Applicant contends that Orkin and Eck are not relevant because the authors discuss problems encountered in identifying an effective vector system and modes of administration, and do not differentiate the utility of a certain vector based on transgene. Applicant further contends that the claims pertain to plasmid vectors that are better characterized, safer and include only desired elements.

This argument has been fully considered but is not deemed persuasive. The efficacy of delivery systems are clearly relevant to whether any given construct comprising any given transgene can be used for gene replacement. For example, some transgenes might require high-

level expression for an extended period in a large number of cells of an organism in order to achieve effective gene replacement while others might require expression in certain cells in a regulated fashion. The unpredictable nature of gene delivery technology is relevant to an analysis of enablement for claims that broadly encompass gene replacement using any therapeutic gene sequence because the effective use of any therapeutic is dependent on ones ability to deliver the therapeutic to the proper location in a sufficient amount for a sufficient period of time. Applicant's assertion that the claims pertain to plasmid vectors that are better characterized, safer and include only desired elements is not persuasive because, aside from the particular promoter sequence comprised by the vector, the claims are very broad and are not limited to comprising any elements that were not well known at the time Orkin was published.

Applicant dismisses the teachings of Rubanyi because the difficulties described by Rubanyi are not directed to custom design of plasmids. Applicant acknowledges that Rubanyi teaches difficulties in matching therapeutic protein to disease and gene delivery vector to match disease but contends that the teachings do not imply that using an optimized plasmid for producing hormones enzymes or proteins "or any other molecules that are secreted into the blood stream would be 'unpredictable'". (Sentence bridging pages 18-19.) However, it is first noted that the claims are not limited to encoding proteins that are secreted into the blood stream. Furthermore, considerations such as difficulties in matching therapeutic protein and gene delivery vector to disease are relevant to the instant claims because they are generic to any therapeutic gene sequence with the intended use in gene replacement.

Applicant dismisses Schwaab, stating that the problems described therein are routinely encountered in protein replacement therapy. However, Schwaab was cited as part of a general

discussion illustrating the fact that the use of each vector comprising a distinct "therapeutic gene sequence" for the stated purpose of "gene supplementation" presents unique challenges and the state of the relevant art is not such that enablement for use of any given therapeutic gene sequence in plasmid mediated gene supplementation evidences enablement for use of any other therapeutic gene sequence fro plasmid mediated gene supplementation. This point is clear from the art considered as a whole.

Likewise, Applicant dismisses the teachings of Rissanen, Emanueli and MacColl on the grounds that the instant claims relate to new, better-designed plasmids which solve the problems of the art. However, as discussed above, the claimed plasmids are highly generic aside from the recitation of a particular promoter sequence and the requirement that the therapeutic gene sequence comprise a single species-specific codon modification. There is no evidence that the elements recited for the claimed plasmid would overcome the unpredictability, which is undeniably present in the gene therapy art, such that the claimed invention is enabled for "plasmid mediated gene supplementation" irrespective of the therapeutic gene sequence comprised by the vector.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C.§112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

Claim Rejections - 35 USC § 112, second paragraph

Claims 1-20 **stand rejected** under 35 U.S.C. 112, second paragraph, as indefinite in being directed to a synthetic mammalian expression plasmid comprising "a codon-optimized-

eukaryotic therapeutic gene sequence". This rejection is maintained for the reasons of record and the reasons set forth herein below in the response to Applicant's arguments.

Response to Arguments

In response to the *prima facie* rejection of record, Applicant has amended claim 1 such that claim is directed to a "plasmid for plasmid mediated gene supplementation in a species comprising...a codon-optimized-eukaryotic therapeutic gene sequence having at least one codon modification specific to the species..." In the remarks, Applicant contends that, even though the specific species is not identified, it is clear that the optimization is particular to the species being targeted for the plasmid mediated gene supplementation. Applicant urges that a person of skill in the art would obviously know which species upon which he or she is intending to use the plasmid mediated gene supplementation and therefore would be able to pick out the optimized plasmid for that species.

This argument has been fully considered but is not deemed persuasive. The instant claims are directed to a product. Therefore, the relevant question with regard to anticipation or infringement is whether a given product has the same structural characteristics as the product claimed. As written, the structural characteristics of the claimed invention depend on the species into which the skilled artisan intends to introduce the plasmid, which is not defined in the claim. The problem that arises is that it is not possible to determine whether a given sequence is within the scope of the claims unless one knows the intentions of the person making or using the plasmid. For example, if, for the sake of argument, CAT was the predominant histidine codon in humans and CAC was the predominant codon in bovine, the skilled artisan would not know

whether a given therapeutic gene sequence comprising a CAT codon is within the scope of the codon-optimized-eukaryotic therapeutic gene sequence of the claims unless he knew whether the sequence was going to be used in humans or cows. In other words, a given therapeutic gene sequence might be inside or outside of the claim scope depending upon the intentions of the person making or using the sequence.

Applicant contends that the facts in the instant case are analogous to the facts in *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, where the Federal Circuit found that claims to a collapsible pediatric wheelchair sized to fit between the doorframe and the seat of an automobile were definite even though the claims did not pertain to a specific automobile. Applicant contends that, similar to the claims in *Orthokinetics*, the current claims do not have to spell out each possible host organism to be definite because a person of ordinary skill in the art will be able to identify the desired species and locate the optimized codons for that species.

These arguments have been fully considered but are not deemed persuasive. The critical difference between the instant claims and the claims of *Orthokinetics* is precisely that the wheelchair claimed in *Orthokinetics* encompassed a chair sized to fit between the doorframe and the seat of an (i.e., any) automobile. Therefore, so long as the chair would fit between the doorframe and seat of any automobile, the chair is within the scope of the claims. In contrast, the determination of whether a given therapeutic gene sequence is within the scope of the instant claims depends upon what the skilled artisan intends to do with the plasmid. In other words, the instant claims are more analogous to a claim to a wheelchair sized to fit between the doorframe and the seat of an automobile that the owner intends to drive. In that case, a given chair might be inside or outside of the claim scope depending upon the intentions of the chair's owner. Clearly,

the possibility that the same product can be inside or outside of the claim scope depending on how or where one intends to use the product renders the scope of the claim indefinite.

Claim Rejections - 35 USC § 102

Rejection of claims 1, 2, 5, 7-9, 11 and 14-20 under 35 U.S.C. 102(b) as being anticipated by Draghia-Akli et al. (1997) *Nature Biotechnol.* 15:1285-1289 (made of record in the IDS filed 14 November 2003) as evidenced by the attached plasmid map for pBS (available at www.stratagene.com/vectors/maps/pdf/pbs.gif) is **withdrawn** in view of the amendment of claim 1 such that the claimed vector must comprise a promoter comprising SEQ ID NO: 15.

Rejection of claims 1, 2, 5, 7-9, 11 and 14-20 under 35 U.S.C. 102(e) as being anticipated by Schwartz et al. US Patent No. 6,423,693 (made of record in the IDS filed 12 July 2004; hereinafter Schwartz '693) as evidenced by Draghia-Akli et al. (*supra*) and the attached plasmid map for pBS (*supra*) is **withdrawn** in view of the amendment of claim 1 such that the claimed vector must comprise a promoter comprising SEQ ID NO: 15.

Claims 1-9 and 11-20 **stand rejected** under 35 U.S.C. 102(e) as being anticipated by Schwartz et al. US Patent No. 6,551,996 (made of record in the IDS filed 14 November 2003; hereinafter Schwartz '996). This rejection is maintained for the reasons set forth in the 24 August Office Action at pages 18-20 and herein below in the response to Applicant's arguments.

Claims 1-9 and 11-20 **stand rejected** under 35 U.S.C. 102(b) as being anticipated by Schwartz et al. (February 2001) WO 01/06988 (hereinafter Schwartz '988) as evidenced by

Schwartz et al. '996 (*supra*) for the reasons set forth in the 24 August Office Action at page 20 and herein below in the response to Applicant's arguments.

As described in the previous Office Action, in Example 1, commencing at page 26, the instant specification describes the construction of an optimized plasmid backbone using as the starting material the plasmid pSP-HV-GHRH having the backbone pAV0125, which the disclosure teaches was described in US Patent No. 6,551,996 (i.e., Schwartz '996). (See especially ¶0084). The instant application summarizes the changes made in the pAV0125 plasmid of Schwartz '996 in ¶0088 and in ¶0089 teaches the elements comprised by the product vector pAV0201. Based on this description, it can be inferred that the pAV0125[1] vector of Schwartz '996 comprises the following elements: the hGH poly A signal, the c5-12 synthetic eukaryotic promoter (which promoter comprises SEQ ID NO: 15; see especially ¶0084, ll. 8-10 of the instant specification); the pNEO prokaryotic promoter and a transposon fragment ("Tn5'); one NEO ribosome binding site; and a pUC18 origin of replication. Furthermore, Schwartz '996 teaches that the pSP-HV-GHRH vector comprises an optimized GHRH coding sequence. (See especially Examples 2 and 8.) Thus, in view of the evidence of record, the skilled artisan would conclude that the pSP-HV-GHRH vector of comprises each of the elements recited in claims 1-9 and 11-20. It is noted that, although Schwartz '996 does not disclose specific sequence for the pUC18 ori (claim 4), the RBS (claim 6), the hGH polyA sequence (claim 8), the PNEO promoter (claim 13) or kanamycin gene (claim 14), given that the working example in the instant case was derived from the vector of Schwartz '996, it is presumed, absent evidence to the contrary, that

the sequence of the elements recited in the instant claims is the same as the sequence of those same elements in the pSP-HV-GHRH vector of Schwartz '996.

Finally, although it does not appear that the pSP-HV-GHRH plasmid comprises an ARS as recited in claim 3, Schwartz '996 teaches at col. 13, ll. 28-28 that the vectors contemplated therein might comprise an ARS as an alternative to an origin of replication.

In view of the foregoing, the skilled artisan would conclude that the vector of Schwartz '996 is the same as the vector of the instant claims. Therefore, the claims are anticipated by Schwartz '996. It is further noted that, because the disclosure of Schwartz '988, at least with respect to the working examples, appears to be identical to the disclosure of Schwartz et al. '996, the claims are also anticipated under 35 USC §102(b) as anticipated by Schwartz et al. '988.

Response to Arguments

In response to the *prima facie* rejection of record, Applicant contends that the art does not anticipate the amended claims because claim 1 has been amended to require that the synthetic mammalian expression plasmid is intended for plasmid mediated gene supplementation in a particular species and that the codon-optimized-eukaryotic therapeutic gene sequence in the plasmid has at least one codon modification specific to the species. Applicant contends that the Schwartz references do not describe that kind of optimization.

This argument has been fully considered but is not deemed persuasive. As described above, the requirement that the therapeutic gene sequence comprise a codon modification specific to the species into which one intends to introduce the vector is indefinite. However, the broadest reasonable interpretation of the claim limitation is that the codon optimized mammalian

[1] It should be noted that Schwartz '996 does not explicitly refer to a vector pAV0125, but does disclose the plasmid

therapeutic gene sequence is produced by a process in which at least one species-specific codon is modified. As such, the codon optimized mammalian therapeutic gene sequence of the claim is viewed as product defined by the process of its production.

Determination of the patentability of a product-by-process claim is based on the identity of the product, not its method of production. If the product in the product-by-process claim is the same (or obvious) from a product of the prior art, the claim is unpatentable, even if the product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). When assessing patentability, the product-by-process claim has potential patentability when the manufacturing steps impart identifiable, distinctive structural characteristic to the final product. In the instant case, an optimized codon is the same regardless of whether that codon was modified relative to some other sequence, which in the instant case is also undefined, or is present in unmodified form. Therefore, the recitation that the mammalian therapeutic gene sequence comprises at least one species-specific codon modification does not distinguish the claimed invention from the vector disclosed in the Schwartz references. In particular, it is noted that the Schwartz references teaches that the pSP-HV-GHRH comprises a nucleic acid encoding a porcine GHRH sequence is intended for use in a pig. (See Example 8.) As the porcine sequence has evolved for expression in pigs, it is reasonable to conclude that at least one codon is optimized for porcine expression. Therefore, it is also reasonable to conclude that the synthetic mammalian expression plasmid of Schwartz et al. comprises all of the elements of the expression plasmid presently claimed.

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pSP-HV-GHRH (see, e.g., Example 8), which the instant application teaches comprises the pAV0125 backbone.

Double Patenting

Rejection of claims 1, 2, 5, 7-9, 11 and 14-20 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,423,693 (Schwartz '693; *supra*) as evidenced by Draghia-Akli et al. (*supra*) and the attached plasmid map for pBS (*supra*) is **withdrawn** in view of the amendment of claim 1 such that the plasmid is limited to comprising SEQ ID NO: 15.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 and 11-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Schwartz '988 (*supra*) or Schwartz '996 (*supra*) in view of Miller et al. US Patent No. 6,924,365.

Applicant has amended the claims to recite that the claimed vector is to be used for plasmid mediated gene supplementation in a species and comprises a codon-optimized-eukaryotic therapeutic gene sequence having at least one codon modification specific to the species. Applicant contends that the eukaryotic therapeutic gene sequence of Schwartz '988 or Schwartz '996 is not "optimized by design and synthesized to be species specific." As discussed above, it is the Office position that the teachings of Schwartz '988 and Schwartz '996 meet the limitations of the claims because the porcine sequence used in their vector is optimized for expression in pigs and it is irrelevant how the optimization was carried out (i.e., by laboratory mutagenesis or by natural selection). However, in the interest of compact prosecution, this rejection is set forth in order to demonstrate that even if one were to accept Applicant's contention that the claimed invention requires that the eukaryotic therapeutic gene sequence be "optimized by design" the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. This rejection should in no way be construed as an admission that the rejections under 35 U.S.C.§102 are not fully supported by the record.

As described above, Schwartz '988 and Schwartz '996 teach a vector comprising all of the elements of the vector presently claimed. Furthermore, both Schwartz '988 and Schwartz '996 contain the teaching, "One skilled in the art recognizes that a variety of nucleotide sequences can be used to encode SEQ ID NO: 1 [the porcine GHRH coding sequence]. The

specific sequence to be used is partially determined on specific sequences to be modified and the experimental conditions determined by the skilled artisan for the specific use. As shown herein the skilled artisan can use a GHRH cDNA sequence for site-directed mutagenesis to create changes in the sequence to contain both the native or species-specific sequence and the desired amino acid substitutions for protease resistance, *etc.*" (Schwartz '988, p. 13, ll. 12-19 and Schwartz '996, ¶ bridging col. 8-9.) Thus, Schwartz '988 and Schwartz '996 both teach modification of the sequence encoding the polypeptide set forth as SEQ ID NO: 1 and contemplate creating changes in the sequence such that it contains species-specific sequence. However, Schwartz '988 and Schwartz '996 do not explicitly teach that the changes made should provide an "optimized codon" as that term is described in paragraph 0055 of the instant application.

Miller et al. teaches the design and production of synthetic nucleic acid sequences which encode a protein wherein at least one non-common codon or less-common codon is replaced by a common codon in an organism. (See especially the Abstract and the discussion beginning at col. 8, l. 6.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include substitution of less-common codons with common codons as taught by Miller et al. among the species-specific changes to the sequence encoding SEQ ID NO: 1 as contemplated by Schwartz '988 and Schwartz '996. Motivation to combine the teachings is found in the teachings of Miller et al. In particular, Miller et al. teaches, "[T]he efficiency with which individual mRNA molecules are translated has a strong influence on the stability of the mRNA molecule" (col. 1, ll. 42-45) and "An approach to increasing protein yield using

recombinant DNA technology is to modify the coding sequence of a protein of interest, e.g., Factor VIII or Factor IX, without altering the amino acid sequence of the gene product. This approach involves altering, for example, the native Factor VIII or Factor IX gene sequence such that codons which are not so frequently used in mammalian cells are replaced with codons which are overrepresented in highly expressed mammalian genes. Seed et al., (WO 98/12207) used this approach with a measure of success. They found that substituting the rare mammalian codons with those frequently used in mammalian cells results in a four fold increase in Factor VIII production from mammalian cells." (Col. 2, first full paragraph.) In view of these teachings, one would be motivated to modify coding nucleic acids to include common codons in order to obtain the expected benefit of more efficient translation, greater mRNA stability and higher protein yield as taught by Miller et al.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because site directed mutagenesis to produce silent mutations in protein coding sequences is fully described in the teachings of Miller et al. and was routinely practiced at the time the instant invention was made.

In view of the foregoing, the skilled artisan would conclude that the claimed invention, as a whole, would have been obvious at the time the invention was made. Therefore, the claims are properly rejected under 35 U.S.C.§103(a).

Allowable Subject Matter

Claim 29 is allowed.

Claim 24 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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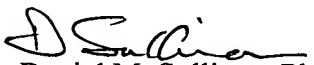

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